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October 19, 1992
10/19/92 G. Kanagasi
DATE NAME

6485/06895

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: G. SANTUS, ET AL.

Serial No.: 07/875,700 Group Art Unit: 1502

Filed: April 29, 1992 Examiner: Hulina

For: THERAPEUTIC COMPOSITIONS FOR INTRANASAL ADMINISTRATION WHICH INCLUDE KETOROLAC

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October 19, 1992

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

RESPONSE AND INFORMATION DISCLOSURE STATEMENT

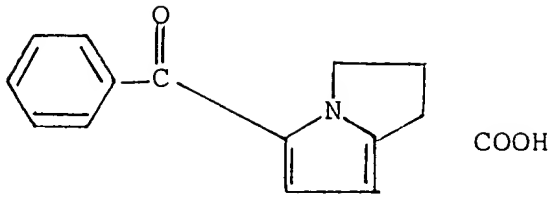
Sir:

In response to the Official Action of July 29, 1992, applicants submit as follows:

In the Claims:

Please add the following new claims:

--19. An analgesic/anti-inflammatory pharmaceutical dosage form which comprises an effective amount of an active ingredient selected from the group consisting of racemic 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, of the formula



optically active forms thereof and pharmaceutically acceptable salts thereof, in combination with a pharmaceutically acceptable excipient or diluent, said dosage form being an intranasally administrable transmucosally rapidly absorbable dosage form achieving effective analgesic/anti-inflammatory blood levels in a host.

20. The dosage form of claim 19 comprising a liquid.

21. The dosage form of claim 20 comprising a mucosal absorption promoter that is not a mucosal irritant.

22. A method for the treatment of inflammatory processes and pain of a traumatic or pathologic origin, which comprises the administration by the intranasal route of a dosage form comprising an effective amount of the active ingredient 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, in a racemic or optically active form or in the form of a pharmaceutically acceptable salt, said dosage form being an intranasally administrable transmucosally rapidly absorbable dosage form, thereby achieving effective analgesic and anti-inflammatory blood levels for said active ingredient.

23. A method according to claim 22 wherein said dosage form comprises said active ingredient is dissolved in an aqueous liquid carrier.

24. A method according to claim 22 wherein said dosage form also comprises a mucosal adsorption promoter that is not a

mucosal irritant.--

REMARKS

Reconsideration of this application and allowance of the claims is respectfully requested.

A. The §112 Rejection

Claims 1-18 have been rejected under 35 U.S.C. § 112 first paragraph. The Examiner contends that the disclosure is limited to intranasal preparations which contain 0.5 - 40.0 mg of KETOROLAC in a concentration ranging from 5-20% (weight/vol.) of the active ingredient. This rejection is respectfully traversed.

Basis for present claim 2 exists in original claim 1 and in the second paragraph of the Summary of the Invention (p. 3, lines 15-21). MPEP § 703.03n specifically supports that the claims are part of the disclosure. Accordingly, it is respectfully submitted that the present disclosure supports and enables the claims. There is no evidence in this record and the Examiner has provided none that formulations containing more or less of the active ingredient could not be made or used. In light of the present disclosure, a person of ordinary skill in the art would have no trouble making intranasally administrable compositions containing KETOROLAC in any intranasally effective amount, i.e. in any amount that would produce an effective blood concentration of KETOROLAC. There is substantial literature on the pharmacokinetics of KETOROLAC. See the references attached to this response and cited in the accompanying Form 1449. In addition, the intranasally administrable KETOROLAC-containing

composition should of course contain a sufficient concentration of the drug so that the effective blood amount can be achieved by the dosage applied intranasally. Thus, a person of ordinary skill would have plenty of guidance from the present disclosure and from the well-established knowledge in this field.

Citation of MPEP § 706.03(z) is believed to be inapplicable in this instance. Unlike novel compounds, the pharmacodynamic and pharmacokinetic properties of KETOROLAC are known. See, e.g., Drugs 39(1): 86-109, 1990, attached. The present invention is directed to a novel dosage form and to a novel method of administration, and gives adequate guidelines and examples as to how to make and use the invention.

B. The § 102(b) Rejection based on Muchowski

Claims 1-3, 5 and 6 have been rejected under 35 U.S.C. §102(b) as anticipated by Muchowski. The Examiner pointed to Example 43 of Muchowski which discloses an oral pediatric form of KETOROLAC. This rejection is respectfully traversed. This Example discloses a suspension of KETOROLAC containing a variety of ingredients that are unsuitable for intranasal administration, such as fumaric acid, sorbitol, Veegum, flavoring, coloring. There is no disclosure whatsoever of an intranasally administrable dosage form. Moreover, there is no suggestion whatsoever that KETOROLAC could or should be nasally administered.

It is significant that Muchowski, which incidentally is the basic patent for KETOROLAC (owned by Syntex Inc. the

developer and marketer of this important drug), is totally silent about intranasal administration. The importance of KETOROLAC was obviously recognized at the time the Muchowski patent was applied for and a diligent effort was made to disclose every dosage form and method of administration that was then thought possible.

For example, Muchowski col. 9:19 - col. 10:14 describes oral and suppository dosage forms. Liquid dosage forms are also mentioned but intranasal administration is conspicuously absent. In addition, Col. 11:35-67, also describes various dosage forms such as oral tablets, vaginal tablets, uterine tablets, suppositories, pills, capsules, and liquid solutions and suspensions for oral or parenteral use. Again, intranasal administration is not mentioned, nor suggested.

Therefore, both Example 43 and the general disclosure of Muchowski show that intranasal administration was not contemplated or suggested for KETOROLAC.

The liquid dosage forms of Muchowski are injectable parenteral dosage forms exemplified by Example 41. In Example 41, the injectable solution contains 10 mg/ml of active ingredient, i.e. 1%. This solution does not contain enough concentration of KETOROLAC to be effective when intranasally administered. If intranasal administration of this parenteral solution were attempted, it would not result in a consistent or effective amount of KETOROLAC being released to the bloodstream. For example, if this solution containing 1% KETOROLAC were sprayed to the nose of a patient, so many "puffs" would be

necessary to deliver enough KETOROLAC to the nose, that the total amount of liquid would exceed the capacity of the nose to hold it and/or would be quickly cleared from the mucosa and thus be ineffective.

The present claims 1-3, 5 and 6 are directed to intranasally administrable dosage forms which means that these dosage forms cannot contain ingredients such as flavoring agents or nasal irritants (e.g. caustic ingredients) and cannot be in tablet, capsule or suppository form. Therefore, the compositions of the present invention are novel because the "intranasally administrable" requirement prevents their being anticipated by the compositions of Muchowski. Moreover, Muchowski contains no teaching that would motivate a person of ordinary skill in the art to make intranasally administrable compositions or to use the claimed nasal administration method (claims 12-18) for which Muchowski does not teach any desirability or expectation of effectiveness.

For at least these reasons Muchowski neither anticipates the present claims nor renders them obvious.

C. The § 102(e) Rejection Based on Ong.

The Examiner has also rejected claims 1, 4, 8-10 under 35 U.S.C. § 102 as anticipated by Ong. This rejection is also respectfully traversed.

The Examiner states that Ong is directed to topical gels for use on skin comprising KETOROLAC, a gel material which can be a carboxymethyl cellulose or polyoxy(propylene/ethylene)

block copolymer and a penetration agent.

However, the skin penetration agents of Ong are known mucosal irritants except for di-isopropyl adipate (DPA). More important, Ong advocates the use in these topical compositions (in addition to the skin penetration agents) of large amounts (35%) of lower alcohols which enhance skin penetration but also render the Ong compositions irritant and therefore not suitable for intranasal administration. It should be emphasized that absorption enhancers for the nasal mucosa need to be much milder than skin penetration agents. The skin penetration agents are believed to act by strongly destructuring the skin (breaking down the skin keratinic layer) and are thus aggressive agents which will irritate the nasal mucosa.

Ong thus does not disclose or suggest intranasal compositions containing KETOROLAC. In the context used by Ong (as supported by the entirety of the Ong disclosure) "topical" means strictly "applied to the skin".

D. The § 102(b) Rejection Based on Baker

Claims 1, 4-9 are rejected under 35 U.S.C. § 102(b) as anticipated by Baker. This rejection is respectfully traversed.

Baker discloses a controlled-release delivery system for periodontal use. The active ingredient (which can be KETOROLAC) is incorporated in a controlled-release polymer matrix particles in turn suspended in a fluid medium. The effect of the Baker composition is to ensure a sustained slow release of the active ingredient for 1-30 days in the periodontal cavity, i.e.

locally not systemically. There is no disclosure or suggestion of systemically active intranasal compositions in Baker (see e.g. Claim 1 of Baker). The effect of the present intranasally administrable dosage form on the other hand is to make KETOROLAC systemically available not locally available. Thus, the present claims by their requirement that the KETOROLAC be intranasally administrable (or administered) exclude local action dosage forms comprising controlled-release matrices of the type disclosed in Baker and the presently claimed compositions are not anticipated by Baker.

Example 11 of Baker is specifically directed to preparation of KETOROLAC-containing controlled-release microspheres for periodontal use. The particular microspheres described in Baker's Example 11 have an <u>in vitro</u> degradation time of 4-5 days. This is too slow for intranasal use with the goal of achieving systemically effective amounts of KETOROLAC.

Nowhere does Baker suggest intranasal use.

E. <u>The § 103 Rejection</u>

Claims 1-18 have been rejected as obvious over the combination of Muchowski, Ong/Baker and Cetenko. Since each of Ong, Baker and Muchowski already discloses KETOROLAC-containing preparations but as discussed above does not teach intranasal administration or intranasally administrable dosage forms, their combination does not supply this teaching. As will be shown, Cetenko is also deficient in this respect and therefore any combination of the foregoing references and Cetenko also fails to

suggest the present dosage forms or method.

Cetenko is directed to novel non-steroidal anti-inflammatory compounds (NSAIDS) which have two moieties: one moiety is derived from the structure of "selected" known NSAIDS (which include KETOROLAC) and is coupled with another moiety derived from hydroxamic acid. The resulting compounds do not bear much overall structural resemblance to KETOROLAC.

Cetenko states that his compounds can be administered intranasally but, contrary to the Examiner's contention, this disclosure does not raise any inference whatsoever about the nasal administrability of KETOROLAC or its effectiveness when thus administered. In fact, one could argue that Cetenko teaches away from intranasal administration of KETOROLAC by stating that a remote derivative of this drug is nasally administrable (and therefore implying that KETOROLAC itself would not be nasally administrable or would not be effective upon such administration).

As it was stated in the present specification (p. 3:31 - p. 4:12):

> Although nasal administration ... is known, it is not to be presumed that all therapeutic agents can be effectively administered by this route. On the contrary, many therapeutic agents cannot.
>
> * * *
>
> The ability of drug molecules to be absorbed by the nasal mucous membrane is utterly unpredictable, as is the ability of intranasal formulations to avoid irritation of the mucous nasal membranes...

Therefore, Cetenko's teaching is limited to intranasal administration of his own hybrid NSAID/hydroxamic acid constructs, and raises no inference as to the intranasal administrability of KETOROLAC or of compositions containing it recited in Muchowski, Ong or Baker.

F. Patentability of the New Claims

The new claims 19-24 are based on the original disclosure as follows: claim 1; p. 6, line 34; p. 3, lines 6-10; p. 4, lines 6-12. These claims even more clearly distinguish over (a) Baker in that claim 19 spells out that rapidly absorbable systemic availability is achieved and claim 20 specifies liquid compositions; and (b) Ong in that the nonirritant nature of the composition excipient/absorption promoters is also specified in claim 21. Claim 20 is restricted to a liquid (not gel) form, which is preferred.

Method claims 22-24 contain the same elements as claims 19-21 except they are based on claim 12 instead of claim 1. (See discussion of method claims below.)

G. The Method Claims

Regardless of whether the composition claims are patentable, the method claims clearly are. There is no suggestion in any reference that nasal administration of KETOROLAC would or should be effective, or that it would be well-tolerated by the nasal mucosa.

H. Information Disclosure

In compliance with the duty of disclosure the documents

cited in the attached Form 1449 are being submitted accompanied by the requisite fee of $200. Please charge any deficiency or credit any excess in this fee to Deposit Account No. 04-0100.

It is requested that each document cited (including any cited in applicants' specification which is not repeated on the attached Form PTO-1449) be given thorough consideration and that it be cited of record in the prosecution history of the present application by initialing on Form PTO-1449, so that it will appear on the face of the patent issuing on the present application, even if the Examiner does not consider it sufficiently pertinent to use in a rejection, or otherwise does not consider it to be prior art for any reason, or even if the Examiner does not believe that the guidelines for citation have been fully complied with.

The present Disclosure Statement is also being submitted in compliance with 37 C.F.R. § 1.56 as an Examiner might consider any cited document important in deciding whether to allow the application to issue as a patent, but the citation of each document is not to be construed as an admission that such document is necessarily relevant or prior art. No representation is intended that the cited documents represent the results of a complete search, and it is anticipated that the Examiner in the normal course of examination, will make an independent search and will determine the best prior art consistent with 37 C.F.R. §§ 1.104(a) and 1.106(b), and in the course of such search will review for relevance every document cited on the attached form even if not initialed.

I. Submission of Certified Copy of Priority Document

A copy of Italian Application MI91 A 002024 duly certified is being submitted. Acknowledgement of this submission is requested.

Based upon the above remarks, reconsideration of this application and issuance of a Notice of Allowance for the subsisting claims is earnestly solicited.

Respectfully submitted,

Adda C. Gogoris
Reg. No. 29,714
Attorney for Applicants

DARBY & DARBY P.C.
805 Third Avenue
New York, New York 10022
(212) 527-7700

Enclosures: PTO Form 1449
Information Disclosure Statement
References - 14
Certified Copy of Priority Document
Check for $200.00

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